



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and  
Research  
1401 Rockville Pike  
Rockville MD 20852-1448

JUN 06 2005

By Certified Mail - Return Receipt Requested  
And By Facsimile Transmission

CBER - 05 - 020

**Warning Letter**

Robert W. Hostoffer, DO  
Allergy and Immunology Associates  
1611 South Green Road  
South Euclid, Ohio 44121

Dear Dr. Hostoffer:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from February 9, 2005 to March 2, 2005. FDA investigator Stephen Kilker met with you to review your conduct of a clinical study entitled [REDACTED]

[REDACTED] FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational new drugs.

At the end of the inspection the investigator issued the Form FDA 483, Inspectional Observations, and discussed it with you. We received an undated and unsigned response letter from you on April 11, 2005. We reviewed the inspection report and your letter. Our comments about your letter are provided below.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 312 and 50 (available at <http://www.access.gpo.gov/nara/cfr/index.html>).

The applicable provisions of the CFR are cited for each violation listed below. Some of the violations were not cited on the Form FDA 483, but were evident from the documents that the FDA investigator collected during the inspection.

1. **You failed to protect the rights, safety, and welfare of subjects under your care and you failed to ensure that the investigation was conducted according to the investigational plan and the signed investigator statement. [ 21 CFR § 312.60 ].**
  - A. Of the five subjects you enrolled in the study, four did not meet the eligibility criteria set forth in the protocol as described below:

Subject	Inclusion/exclusion criteria	Result
██████	Inclusion criterion #3 -- evidence of ██████████	No documentation available to verify ██████████
██████	Inclusion criterion #3 -- evidence of ██████████ Based on protocol appendix J, pre-treatment ██████████ must be less than ██████████	Pre-treatment ██████████ were ██████████
██████	Inclusion criterion #9 -- Pharmacokinetic (PK) study: at least 3 months of treatment with repeated doses (every 3 or 4 weeks) of ██████████ prior to entry  Exclusion criterion #1 -- evidence of active infection at time of screening  Exclusion criterion #5 -- ██████████	Started ██████████ every 3 weeks after signing the informed consent. Had been on treatment every 2 weeks.  Frequent sinusitis at screening.  ██████████
██████	Inclusion criterion #9 -- PK study: at least 10 years of age prior to entry  Inclusion criterion #9 -- PK study: at least 3 months of treatment with repeated doses (every 3 or 4 weeks) of ██████████ prior to entry  Inclusion criterion #3 -- evidence of ██████████ --pre-treatment ██████████ to be less than ██████████  Exclusion criterion #5 -- an ██████████	Signed assent for efficacy study on 8/20/01 when subject was 9 years of age.  Initiated treatment with ██████████ on 12/28/01  Normal pre-treatment ██████████  Pre-existing ██████████

In your letter, you acknowledge the lack of documentation of pre-treatment ██████████ for subject ██████████ and explained that subject ██████████ lacked documentation of pre-treatment ██████████. However, our inspection found documents that show that subject ██████████ had normal pre-treatment ██████████ and thus was ineligible for the study.

For subject ██████████ you explain in your letter that you did not think this subject was affected with ██████████ at the time of enrollment, and that earlier symptoms had resolved. We disagree. The subject's medical history included this diagnosis and you failed to produce

documentation that the condition had been resolved before enrollment. We note that during the inspection you and the FDA investigator discussed the [REDACTED] experienced by subject [REDACTED] as [REDACTED]. In your letter you explain that [REDACTED] ".....may be considered as an infectious etiology...." The protocol excludes subjects with evidence of active infection at screening from the study.

You acknowledge the protocol deviation of enrolling subject [REDACTED] with sinusitis and subject [REDACTED] at nine years of age.

- B. The protocol version dated 7/10/01 indicated a 16 and 15 month study duration for the subjects enrolled under the PK study and efficacy study, respectively. Each study had an 11-week wash-in/wash-out (W/W) phase followed by a 53-week efficacy phase. You failed to follow this protocol requirement in that three of the five enrolled subjects received additional doses of study drug in the W/W phase that exceeded the protocol limits, as shown in the following table.

Subjects with extra visits	Additional infusions in W/W phase
[REDACTED]	At least 2
[REDACTED]	At least 3
[REDACTED]	At least 2
[REDACTED]	At least 6

- C. The protocol required blood to be drawn at indicated time points during [REDACTED] study drug infusion to evaluate study parameters such as intravascular exposure to [REDACTED]/study drug and for [REDACTED] measurements. You failed to collect blood samples or collected them incorrectly for subjects [REDACTED] and [REDACTED] on more than six occasions and for subjects [REDACTED] and [REDACTED] on more than one occasion.

In your letter, you acknowledge the deficiencies in the study conduct regarding blood sampling. You propose to conduct future studies according to the protocol and document such protocol deviations with explanations.

- D. You failed to report a serious adverse event (SAE) to the sponsor and the Institutional Review Board (IRB) in a timely manner. Subject [REDACTED] was hospitalized for one day on [REDACTED] for a [REDACTED] episode with symptoms of vomiting and abdominal pain. The protocol required SAEs to be reported to the sponsor by telephone within 24 hours and in writing

within five working days. Records indicate this SAE was reported to the sponsor on 9/4/03, and to the IRB on 1/12/04, after the study ended.

In your letter, you acknowledge the observation, and explain that this episode occurred while the subject was under the care of another physician at another facility. You committed to promptly report SAEs to the IRB in the future.

- E. The protocol required the dosage of the [REDACTED] comparator drug for the PK study to be between [REDACTED]. Subjects [REDACTED] did not meet this requirement as the [REDACTED] doses were, [REDACTED] and [REDACTED] respectively.

In your letter, you acknowledge these doses and explain that you did not consider them as protocol deviations. As you state in your letter, the protocol does suggest a range to maintain high [REDACTED] but the range is between [REDACTED] not between [REDACTED]

- F. The protocol required that [REDACTED] a serious bacterial infection and a primary endpoint of the study, be diagnosed with [REDACTED]. You failed to perform an [REDACTED] for subject [REDACTED] to confirm the diagnosis of [REDACTED] on 5/3/02.

In your letter you agree that no [REDACTED] was performed for this subject and indicate that the subject was treated based on clinical diagnosis.

- G. You failed to perform the 12-lead EKG during the screening visit on 12/6/01 for subject [REDACTED] as required by the protocol. You performed the EKG on 12/26/01.
- H. The protocol required the infusion of [REDACTED] two to four weeks after the performance of screening evaluations and signing the informed consent forms. Subject [REDACTED] was administered the [REDACTED] more than two months after the screening and signing the informed consent.
- I. The protocol required that weekly subcutaneous doses of the study drug be divided over one to four injection sites depending on the volume administered. On many occasions there were more than four injections sites, such as for subject [REDACTED] who received study drug through 12 injections at six sites on 1/24/03.
- J. You failed to collect the paper diary or electronic diary data as required by the protocol. The protocol stated that the paper diary was to be reviewed during the subject's periodic visits with the clinical investigator (every 3-4 weeks) and that the electronic diary data were to be downloaded each

night and available for the investigator's review which will then be electronically transferred to the sponsor. Although the electronic diary for subject [REDACTED] was not functional from March through September 2003, there is no evidence that you collected the information about the safety of the study drug during this period.

- K. You failed to identify all sub-investigators on the Form FDA 1572. [REDACTED] participated in the study for subjects [REDACTED] respectively.

**2. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [ 21 CFR § 312.60 ].**

You obtained informed consent/assent from subjects or subject's legally authorized representative (LAR) using (1) an incorrect consent form that did not accurately describe the study procedures, and/or (2) an outdated consent form. Informed consent from the subject or the subject's LAR and assent of minor subjects is not legally effective if the forms are signed after the study procedures were initiated, if the wrong procedures are described, or if the forms are obsolete or incomplete. The IRB-approved consent forms required your dated signature for each subject. The following table illustrates the deficiencies noted in the informed consent process for the five subjects at your site.

Subject	Signature date of informed consent (IC) or assent	Informed consent deficiencies
[REDACTED]	11/6/01-- LAR signed the IC	LAR signed the obsolete 4/17/01 version. After 3 months in the study LAR signed the correct (7/26/01) version on 2/14/03.
	2/14/03 -- LAR signed the IC	LAR Signed the 11/5/02 version for the extension study containing the incorrect investigator name [REDACTED]
	3/21/03 -- LAR signed the IC	Two months after the additional blood draws were initiated LAR signed the 12/10/02 version for additional blood draws.
[REDACTED]	12/6/01 -- subject signed the incorrect PK IC	Efficacy-only subject signed the incorrect (PK IC) and obsolete (4/17/01 version) IC; you signed on 8/16/02.
	12/23/02 -- subject signed the efficacy IC	After one year in the study subject signed the efficacy IC, 12/4/01

		version. Instead of your name, [REDACTED] is noted as the clinical investigator; [REDACTED] signed on 12/23/02.
[REDACTED]	12/7/01-- subject signed the efficacy IC  2/21/03 -- subject signed the correct PK study IC  2/21/03 -- subject signed the PK addendum for the extension of the study	This PK subject signed the obsolete (4/17/01 version) and incorrect (efficacy) IC  After 14 months in the study, the subject signed the correct PK study IC, (7/26/01 version); the coordinator conducting discussion signed one week later on 2/28/03 and you signed on 3/24/03  Subject signed the 11/5/02 version for extension containing the incorrect investigator name [REDACTED] you signed the IC on 3/24/03
[REDACTED]	8/20/01-subject signed the incorrect assent  3/13/03 -- subject signed the correct PK study assent  Consent for PK substudy addendum was not obtained from subject and LAR	PK subject signed the incorrect efficacy assent when the subject was 9 years old  After one year in the study subject signed the correct PK study assent; you signed the IC on 3/24/03  Subject/LAR did not sign the IC for the extension of the study; six months after the study completion by the subject on 2/3/04 you stated the deficiency in a letter to the Institutional Review Board (IRB)
[REDACTED]	6/17/02 -- subject signed an obsolete assent form  3/27/03 -- subject signed the correct assent form	Signed the obsolete 4/17/01 version assent; the coordinator dated the subject and LAR signatures as "6/17/02"  Nine months later the subject signed the correct 7/26/01 version assent; the coordinator dated the signatures as 3/27/03 as stated in your note to file dated 2/2/04

In your letter, you acknowledge the deficiencies in the informed consent process and describe the complicated nature of the study. You explain that subjects were verbally informed about the study procedures to be performed. You are responsible for documenting that the subjects or their

legally authorized representatives were informed of the study procedures before any study related procedures were performed.

**3. You failed to maintain adequate records of the disposition of the drug.  
[ 21 CFR § 312.62(a) ].**

A. The protocol required that records of self-administration of study drug at home were to be collected and that all used and unused containers of study drug were to be accounted for. You did not maintain adequate records for the disposition of the study drug as illustrated in the following examples:

- i. The amount of study drug received at home by all subjects cannot be accurately determined. The residual volume in the cassette was not measured when the drug cassettes were returned by the study subjects. The dosage volume and the number of doses were printed on each peel-off label attached to the drug cassettes that were shipped by the central pharmacy. The drug accountability records note that "residual consistent with overfill" and does not indicate the amount of residual volume left in the cassette.
- ii. Drug accountability records note that some cassettes could not be accounted for, some drug inventory records did not document the destruction of drug cassettes, and some returned cassettes had no labels as shown in the following table:

Subject	Study phase	Number of cassettes	Comments
[REDACTED]	W/W	11	No record of return and destruction
	Efficacy 54	1	No record of return and destruction
[REDACTED]	W/W	2	Not reconciled
	Efficacy doses 41 to 53	13	Labels not brought back by subject and are missing
[REDACTED]	Efficacy doses 25 to 58	At least 30	Numerous unexplained corrections to dates the site verified the drug label log

B. The protocol required administration of the study drug by the subject or a trained caregiver at home after at least 2 supervised administrations. For subject [REDACTED] the number of doses of study drug administered at home cannot be accurately determined. The peel-off labels collected at the site indicate that subject [REDACTED] was shipped six doses of study drug between

7/25/02 and 8/11/02 for three weekly infusions. You failed to maintain records regarding the study drug doses for this subject who was shipped three extra doses.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies. Your response should include any documentation necessary to show that correction has been achieved.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include clinical hold of ongoing studies, injunction, and initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs.

Please send your written response to:

Ms. Bhanu Kannan  
Division of Inspections and Surveillance (HFM-664)  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Suite 200N  
Rockville, Maryland, 20852-1448  
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



Mary A. Malarkey  
Director  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research



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CC:

Carol Heppe, District Director  
Food and Drug Administration  
6751 Steger Drive  
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William C. Jacobs, Chairman  
Western Institutional Review Board  
3535 Seventh Avenue SW  
Olympia, Washington 98502